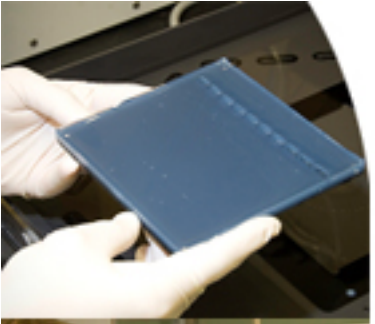

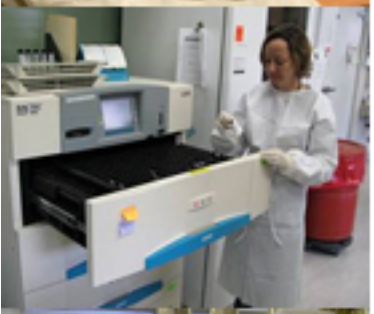


Exploring Novel Approaches to Shared TB Laboratory Services:

California-Wisconsin Shared Services Pilot Study

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Outline

- Background and Objectives of the Shared Services Project
- Logistics of the Project
- Testing involved
- Results
- Conclusions

Background

- Although tuberculosis (TB) remains a significant burden to public and private health care organizations nationwide, the number of TB cases continues to decrease[1]
- For laboratories in areas that are low-incidence for TB, it may be a struggle to offer a full spectrum of TB laboratory services in the face of ever-decreasing test volumes.
- Ongoing budgetary concerns and retirement of experienced laboratory professionals contribute to this struggle.

Background

- To maintain quality laboratory testing and to control expenses, laboratories may consider a variety of shared service options
  - Referral for specialized testing
  - Laboratory partnerships
- Laboratories are hesitant to explore these opportunities, as many aspects of shared laboratory services have not been fully examined.

Objectives of Shared Services Pilot

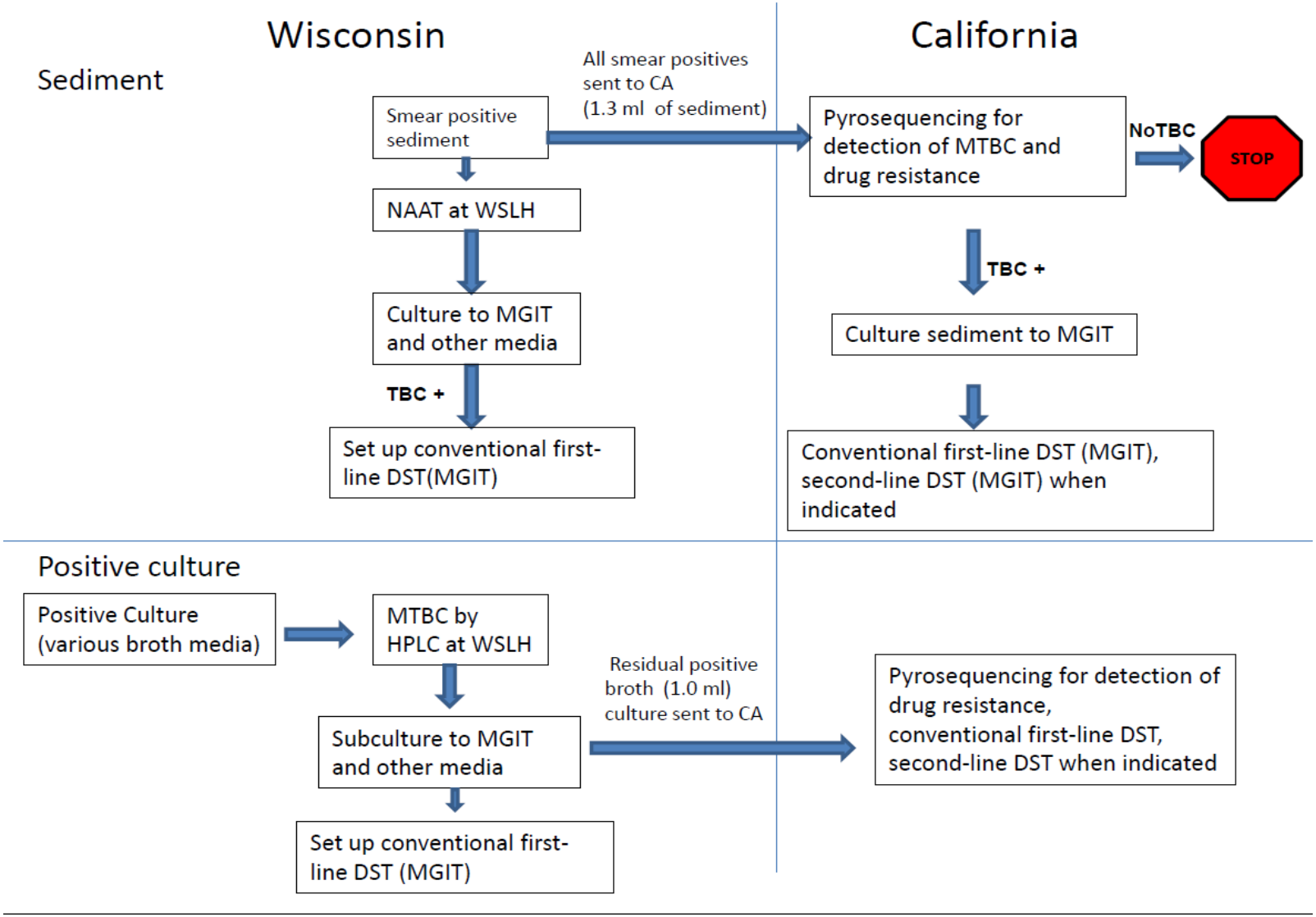
- Assess feasibility and consequences of referring smear-positive sediments to a reference laboratory for detection of TB by NAAT.
- Assess utility of universal referral of sediments and cultures for rapid molecular detection of drug resistance for a population at low risk for drug resistance.
- Assess feasibility and consequences of referring MTBC-positive sediments and cultures to a reference laboratory for conventional first- and second-line DST.

Shared Services Project

- Wisconsin State Laboratory of Hygiene (WSLH) referred specimens to the California Department of Public Health Laboratory (CDPHL)
  - Nucleic Acid Amplification Testing (NAAT)
  - Detection of drug resistance by molecular methods (PSQ=pyrosequencing)
  - Conventional TB first- and second-line drug susceptibility testing (DST)
- Wisconsin performed parallel NAAT and conventional TB first-line DST
- Nine-month study period (9/1/12 to 5/31/13)

Summary of California and Wisconsin Mycobacteriology Services

	CDPHL	WSLH
Nucleic Acid Amplification Testing (NAAT) for detection of *M. tuberculosis* complex	Pyrosequencing, *IS6110*	Laboratory-developed real-time PCR, *IS6110*
Detection of Drug Resistance by Molecular Methods	Pyrosequencing (PSQ) INH (*katG, inhA, ahpC)* rifampin (*rpoB)* fluoroquinolone (*gyrA)* injectables (*rrs)*	Referred to CDC for Molecular Detection of Drug Resistance (MDDR) program[4]
TB first-line DST, Conventional	INH (two concentrations), rifampin, ethambutol, PZA by MGIT	INH (two concentrations), rifampin, ethambutol, PZA by MGIT
TB second-line DST, Conventional	Amikacin, moxifloxacin, ethionamide, and capreomycin by MGIT	Referred to CDC for agar proportion testing


Wisconsin
California
Sediment
All smear positives sent to CA (1.3 ml of sediment)
Smear positive sediment
Pyrosequencing for detection of MTBC and drug resistance
NoTBC
STOP
NAAT at WSLH
TBC +
Culture to MGIT and other media
Culture sediment to MGIT
TBC +
Set up conventional first-line DST(MGIT)
Conventional first-line DST (MGIT), second-line DST (MGIT) when indicated
Positive culture
Positive Culture (various broth media)
MTBC by HPLC at WSLH
Residual positive broth (1.0 ml) culture sent to CA
Subculture to MGIT and other media
Pyrosequencing for detection of drug resistance, conventional first-line DST, second-line DST when indicated
Set up conventional first-line DST (MGIT)

Number of Specimens Referred to CDPHL and Number of Results Reported by CDPHL

Total number of specimens shipped	182
Number of patients with specimens shipped	162
Total number of shipments	90
NAAT: detection of *M. tuberculosis* complex from primary patient sediment	139
Detection of drug resistance (molecular)	47
Conventional TB First-line DST	41
Conventional TB Second-Line DST	13

Results

Submission and Transport Time

Time to Submission (average number of days from receipt at WSLH until send-out to CDPHL for Testing), smear + sediment	**0.877** **Range = 0-5 days**
Average number of days in transit (FedEx or UPS)	**1.13** **Range = 1-5 days**
TOTAL	**2.0 days**

Shipping Costs

Description	Unit Cost	Number of Packages	Total ($)
Category A Shipment	Infectious shipper $15.10 FedEx* overnight $64.12	30	2,377
Category B Shipment	Shipper + cold pack $15 UPS** overnight $19.70	60	2,082
	TOTAL		**$4459**

(*) Federal Express
(**) United Parcel Service

Shipping Summary

- Both FedEx and UPS offered rapid and reliable package transport (average 1.13 days for overnight service).
- Shipping costs were substantial ($4459)
- Estimated labor costs for packaging and shipping would be $50 X 90 = $4500

Detection of TB: Comparison of In-house and Referral Testing

NAAT for detection of *M. tuberculosis* complex (IS6110) from primary patient sediment	WSLH (real-time PCR)	Referral to CDPHL for detection of TB by PSQ
NAAT Results Reported	135	139
Number of culture-confirmed TB patients with positive NAAT from primary sediment	23/29 (79.3%)	27/29 (93.1%)
Average TAT from date of receipt in Wisconsin Lab (days)	0.31 Range = 0-4 days	3.84 Range = 1-11 days
Percent of Results meeting Healthy People 2020 Goal (identification of TB within 48 hours of receipt in WI Lab)	22/29 = 75.8%	7/29 = 24%

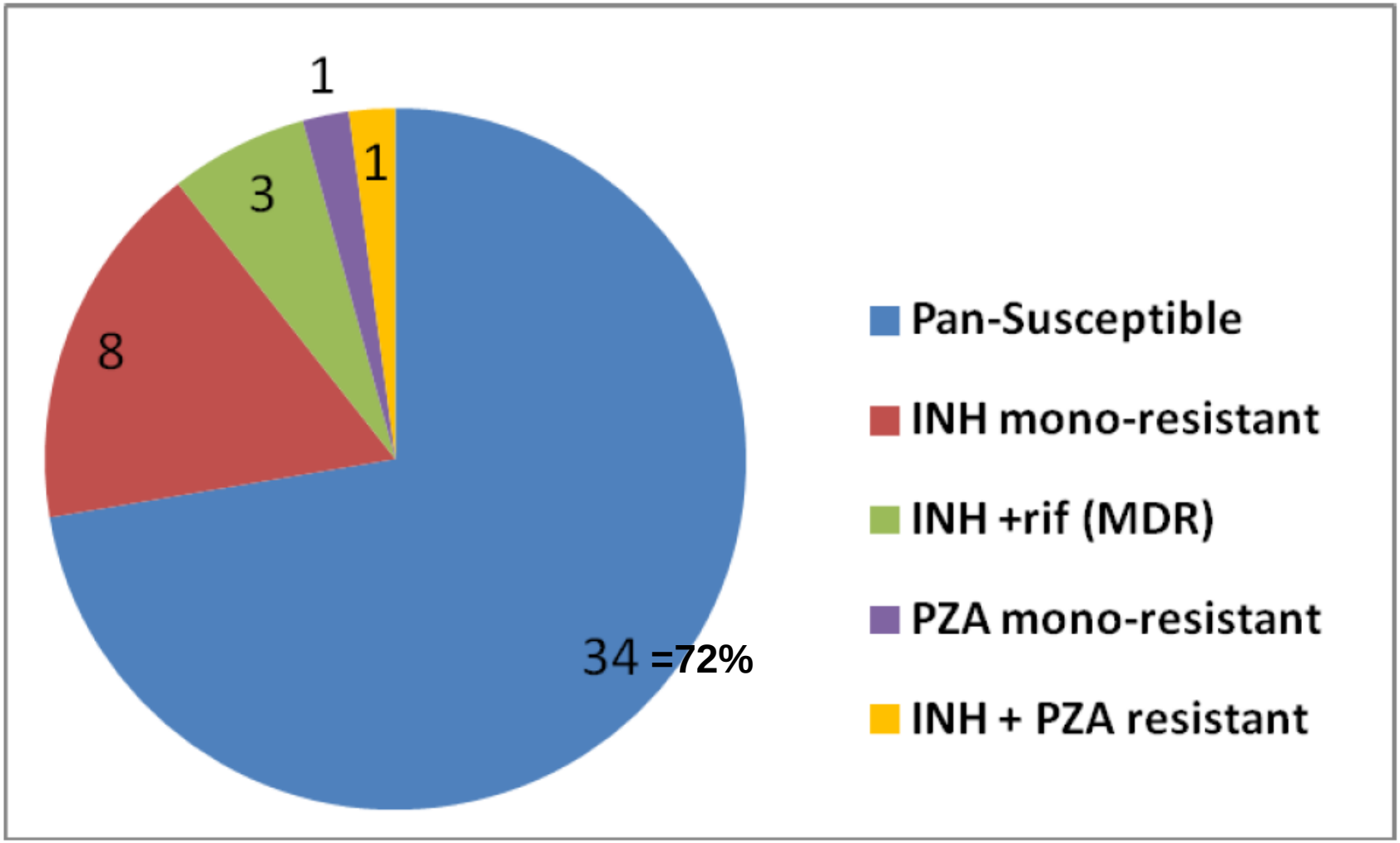
Summary: Referral for Detection of TB

- Although average time to submission for sediments (0.877 days) and average number of days in transit (1.13 days) were short, these delays had a substantial impact on NAAT TAT, despite excellent TAT (1.83 days) for NAAT at CDPHL.
- Only 24% of referred NAATs met the Healthy People 2020 Goal of detection of MTBC within 48 hours of specimen receipt.
- NAAT may not be as conducive to referral as other mycobacteriology testing due to the very short TATs required.

Detection of Drug Resistance

	WSLH	Referral to CDPHL
Average PSQ TAT from date of receipt in Wisconsin Lab (days)	**Not performed**	**3.84** **Range = 1-11**
Median TAT: Conventional TB First Line DST, from date of receipt in Wisconsin Lab (days)	**26** **Range = 14-59**	**42** **Range = 21-114**
Median TAT: Conventional TB Second-Line DST, from date of receipt in Wisconsin Lab (days)	**Not performed**	**41.5** **Range = 27-115**

Drug Resistance Detected



Summary: Detection of Drug Resistance by PSQ

- On average, PSQ results were reported 22 days before in-house conventional TB first-line DST results were complete.
- During the study, three new MDR-TB cases were rapidly identified using molecular testing.
- Based on PSQ results, conventional second-line DST could proactively be set up.
- PSQ results were routinely used by the Wisconsin TB Program to ensure appropriate therapy and patient management.

Use of PSQ results by WI TB Program

- **MDR-TB prediction:**
  - Full panel MDDR testing (including *emb*B and *pnc*A loci) is necessary for therapy decisions of new MDR-TB patients.
  - Continue any "susceptible" 1st line drugs, add fluoroquinolone and injectable
- **INH resistance prediction:**
  - Continue "susceptible" 1st line drugs, lengthen therapy, add moxifloxacin (?)

Use of PSQ results by WI TB Program

- **Pan-susceptible prediction:**
  - Gives TB program first prediction that the patient can be treated with 1st-line drugs
  - Assures nurses to continue standard therapy, even when the patient isn't doing well in the beginning
  - Good QA check for when conventional results are available (not necessary to repeat testing for "resistant" conventional result?)

Referral for Conventional DST

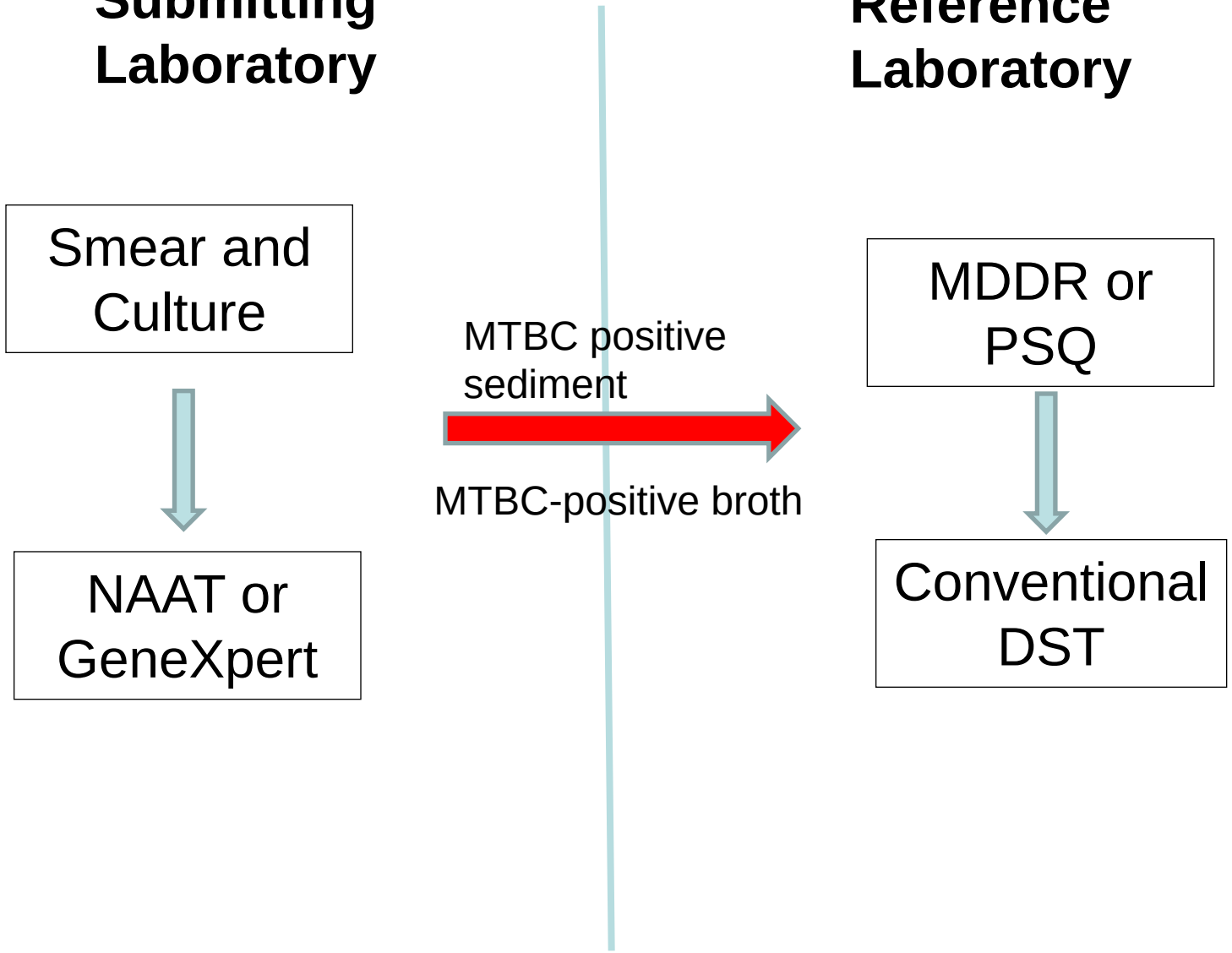
- Referral lead to a 16-day (median) delay in reporting conventional first-line DST results; TAT for referral for conventional TB first-line DST was 42 days.
- The CDPHL laboratory-developed MGIT assay for amikacin, moxifloxacin, ethionamide and capreomycin yielded rapid second-line DST results.
  - Additional drug testing (e.g. PAS, cycloserine, rifabutin) may be required for therapy decisions in some jurisdictions.

Discordant Results

Nature of Discordance	Number of Events
NAAT: false negative in submitting lab, reference lab, or both	7
PSQ results don't agree with conventional results TB first-line DST	3
Conventional TB first line DST results don't agree between submitting lab and reference lab	3

Costs

Description	Unit Cost	Number Performed	Total ($)
NAAT/PSQ	$187	139	25,993
TB First-Line DST by MGIT	$190	41	7,790
TB Second-line DST by MGIT	$200	13	2,600
Packaging and Shipping	See slide 13		8,959
	TOTAL		**$45,342**


Submitting Laboratory
Reference Laboratory
Smear and Culture
NAAT or GeneXpert
MTBC positive sediment
MTBC-positive broth
MDDR or PSQ
Conventional DST

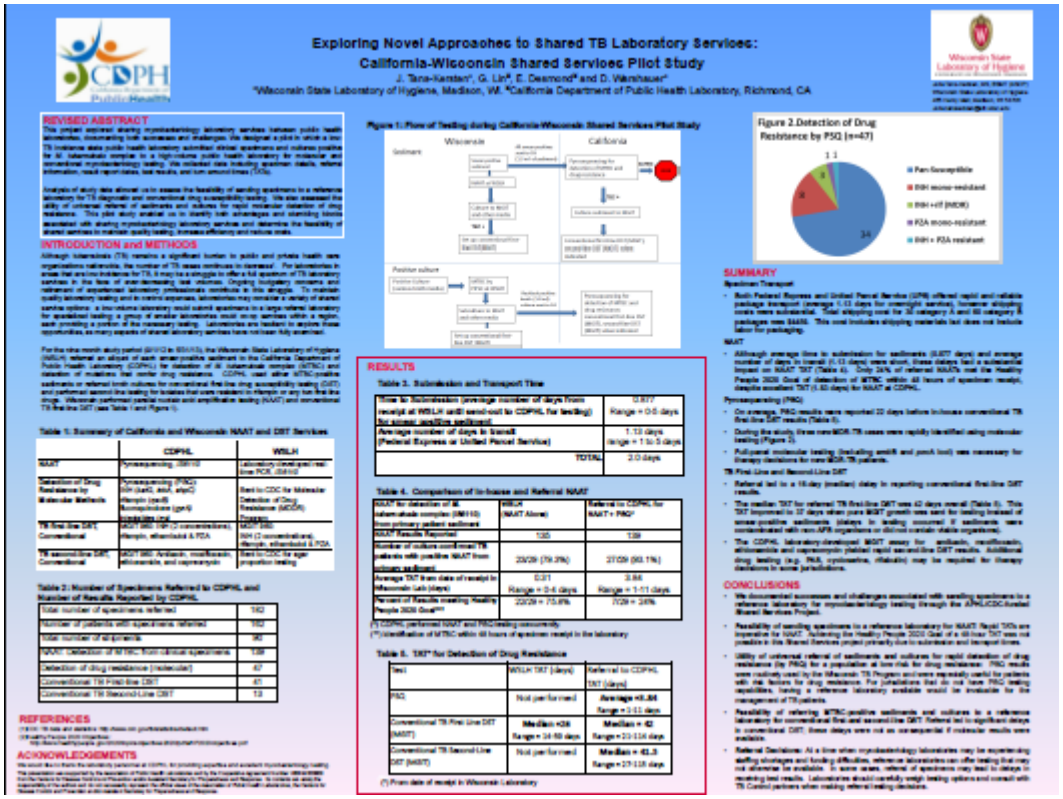
Conclusions

- Through the CDC/APHL-funded Shared Services Project, we documented successes and challenges associated with sending specimens to a reference laboratory for mycobacteriology testing.
- Rapid TATs are imperative for NAAT. Achieving the Healthy People 2020 Goal of a 48-hour TAT was not possible in this Shared Services project.
- Sharing services provided rapid detection of drug resistance by PSQ to Wisconsin patients. These results were valuable for timely patient management decisions.

Conclusions (continued)

- Referral led to significant delays in conventional DST; these delays were not as consequential if molecular results were available.
- Laboratories should carefully consider testing options and consult with TB Control partners when making referral testing decisions.
- At a time when mycobacteriology laboratories may be experiencing staffing shortages and funding difficulties, reference laboratories can offer testing that may not otherwise be available. Benefits of referral testing may outweigh associated costs and delays.

Please see poster #6 for more details!



CDPHL Laboratory Team

<u>A Special Thanks to:</u>
Dr. Ed Desmond
Grace Lin
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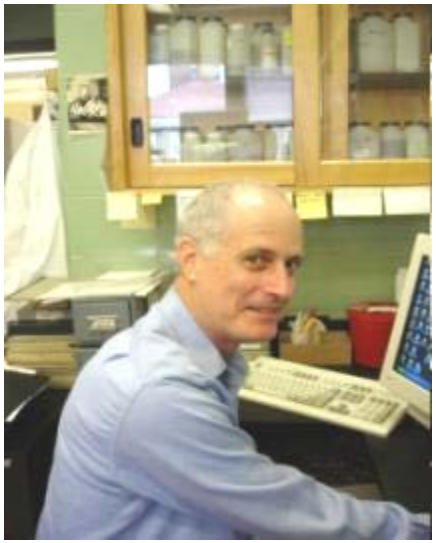
Shantelle Lucas

WSLH Laboratory Team

Nate



Dave

Youngmi and Ana

Julie B.

Don

Julie TK

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(2)Wisconsin TB Program statistics: http://www.dhs.wisconsin.gov/tb/statistics/DocsStatistics/TBCaseByCounty2010.pdf

(3)Healthy People 2020 Objectives: http://www.healthypeople.gov/2020/topicsobjectives2020/pdfs/HP2020objectives.pdf

(4) CDC MDDR Program: http://www.cdc.gov/tb/topic/laboratory/mddr.htm

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